REMARKS

Favorable reconsideration is respectfully requested in view of the above amendments and the following remarks. Following the amendments, claims 175, 176, 178-187 and 189-196 are pending in the application, with claims 175 and 186 being in independent format.

The title of the invention has been amended to read "Generation of Cartilage using Magnetizable Particles."

Claims 177 and 186 have been cancelled from the application. Independent claims 175 and 186 have been amended to: recite the full name of the TREK ion channel; to clarify that the claimed methods result in the generation of cartilage tissue; and to replace reference to "cartilage cells" with reference to "chondrocyte progenitor cells". Support for this amendment may be found, for example, on page 9 lines 11-12 and page 14 lines 12-13, of the specification as originally filed. Claims 178 and 189 have been amended to correspond to amended claims 177 and 186.

It is urged that support for all the above amendments can be found throughout the application as originally filed and that none of the amendments constitute new matter or raise new issues for consideration.

Objections to the Specification

As requested by the Examiner, the title of the invention has been amended to be more clearly indicative of the claimed subject matter.

Claim Rejections under 35 USC §112, Second Paragraph

The pending claims stand rejected under 35 USC §112, second paragraph, as being indefinite. Specifically, the Examiner states that the claims using the acronym TREK without first defining this acronym in the independent claims, and that claims 175 and 186 lack essential steps. As noted above, independent claims 175 and 186 have been amended to recite "TWIK-related potassium channel (TREK)" and to clarify that the claimed method results in the generation of cartilage tissue.

It is submitted that, following the above amendments, one of skill in the art would be able to readily determine the metes and bounds of the pending claims, and that this rejection of the claims under 35 USC §112, second paragraph, may thus be properly withdrawn.

Claim Rejections under 35 USC §112, first paragraph - enablement

Claims 175-196 stand rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure. This rejection is respectfully traversed.

Although the Examiner has acknowledged that the specification is enabling for (1) up-regulation of osteopontin in response to a magnetic field in the presence of anti-TREK antibody bound to magnetic nanoparticles binding to TREK channel in mesenchymal cells, and (2) the production of cartilage matrix proteins in mice by implanted human mesenchymal stem cells in the presence of magnetic nanoparticles bound to cells via an anti-TREK antibody in response to time varying magnetic fields, the Examiner has asserted that the specification does not reasonably provide enablement for:

(A) an *in vitro* method for the generation of cartilage tissue from mammalian cartilage cells expressing mechanosensitive TREK potassium ion channels, and

(B) a method of the generation of new cartilage tissue in a patient, wherein the new cartilage tissue is generated from cartilage cells expressing the mechanosensitive TREK potassium ion channels.

The Examiner has determined that Exhibit B submitted with the Declaration of Dr. Alicia El-Haj on January 8, 2008 (hereinafter referred to as Declaration No. 1), evidences production of cartilage matrix proteins in mice by implanted human mesenchymal cells in the presence of magnetic nanoparticles bound to cells via an anti-TREK antibody. The Examiner asserts that there is insufficient evidence for a method for the generation of cartilage tissue using magnetisable particles bound to an anti-TREK antibody, since the synthesis of cartilage matrix proteins is distinct from the production of cartilage tissue. In this regard, the Examiner indicates that Exhibit B does not provide any evidence for the presence of a ground substance rich in proteoglycan and elastin fibers. The Examiner also states that the human mesenchymal stem

cells disclosed in Exhibit B are not equivalent to the cartilage cells of claims 175 and 186. In conclusion, Examiner is of the view that it would require undue experimentation to practice the claimed invention claimed.

As noted above, claims 175 and 186 have been amended to recite methods that employ "chondrocyte progenitor cells", rather than "cartilage cells". Declaration No. 1 concerns the use of human mesenchymal cells, which are capable of generating cartilage tissue and are a form of chondrocyte progenitor cell. Accordingly, the evidence presented in that Declaration No. 1 is directly applicable to the amended claims.

A further declaration by Dr. El-Haj (Declaration No. 2) is submitted with this response in order to further evidence the generation of cartilage tissue using the presently claimed methods, without undue experimentation.

Declaration No. 2 contains Exhibits 1 and 2 which provide additional experimental data for the Examiner's consideration. In both Exhibits, human bone marrow stromal cells (HBMSCs) are used. These are a type of chondrocyte progenitor cell, consistent with the description on pages 9 and 14 of the present application, e.g. page 9 lines 11-12, where it is stated that "Alternatively, the cells may be chondrocytes and/or stromal cells, such as chondrocyte progenitor cells." (emphasis added).

Thus, limitation of the claims to chondrocyte progenitor cells provides the necessary cellular component for the formation of cartilage tissue. The outstanding issue as regards formation of cartilage tissue is, therefore, whether or not the necessary protein matrix components will be generated when the chondrocyte progenitor cells are used in the claimed methods.

In connection with this, the Examiner indicated that elastin is an essential component of the cartilage protein matrix. As noted in paragraph 12 of Declaration No. 2, the Examiner provides no evidence or source for his conclusion that the presence of elastin fibers is **essential** to determine whether new cartilage tissue has been formed. Whilst Applicants can understand the Examiner's request to demonstrate synthesis of the cartilage protein matrix (which may contain elastin), Applicants do not accept the Examiner's focus on the demonstration of the presence/absence of elastin.

The Examiner highlighted two areas where he considered the specification not to reasonably enable the claimed methods. The first of these was:

(A) an *in vitro* method for the generation of cartilage tissue from mammalian cartilage cells expressing mechanosensitive TREK potassium ion channels.

In this respect, Exhibit 1 of Declaration No. 2 confirms the upregulation of osteopontin from chondrocyte progenitor cells *in vitro* and extends the findings of Exhibit A of Declaration No. 1 to show a significant increase in expression of the cartilage matrix proteins Collagen I, Sox 9, Cbfa 1 and osteopontin (Opn) *in vitro*. Exhibit 1 also demonstrates elevated expression of **proteoglycan** synthesis around chondrocyte progenitor cells *in vitro*.

The evidence provided in Declarations No. 1 and No. 2 is clear in that, *in vitro*, (i) chondrocyte progenitor cells have been used, and (ii) the upregulation in cartilage matrix proteins and proteoglycan synthesis is consistent with the generation of cartilage tissue.

Applicants submit that, taken together, the evidence provided in Declarations No. 1 and No. 2 clearly enables the method of *in vitro* generation of cartilage tissue of claim 176 to be performed without undue experimentation, as this evidence demonstrates the magnetic stimulation of chondrocyte progenitor cells to produce both the protein matrix and proteoglycan components of cartilage tissue.

The second area where Examiner considered the specification not to reasonably provide enablement was:

(B) a method of the generation of new cartilage tissue in a patient, wherein the new cartilage tissue is generated from cartilage cells expressing the mechanosensitive TREK potassium ion channels.

Applicants note that the Examiner has already determined that Exhibit B evidences production of cartilage matrix proteins in mice by implanted human mesenchymal cells in the presence of magnetic nanoparticles bound to cells via an anti-TREK antibody. In light of the amendment of claim 186 to recite "chondrocyte progenitor cells" (such as human mesenchymal cells) this evidence is directly relevant to enablement of the method of claim 186, and Examiner is requested to reconsider.

Exhibit 2 of Declaration No. 2 provides further evidence of enablement of amended claim 186. In particular, in these *in vivo* studies elevated expression of proteoglycan and collagen matrix synthesis around chondrocyte progenitor cells was observed (Exhibit 2, and paragraph 11 of Declaration No. 2) and new chondrogenic tissue formation is demonstrated (Exhibit 2, and paragraph 10 of Declaration No. 2).

Pound et al. (Tissue Engineering Vol. 12 No. 10 (2006) 2789-2799; copy enclosed for the Examiner's convenience) demonstrates that the inventors' experimental approach is art accepted. In particular, Pound et al. confirms that the alginate capsule model reported in Declaration No. 2 is art accepted (see e.g. abstract, page 2790 left col. lines 16-19, page 2798 beginning of final paragraph).

In summary, the Examiner has indicated that the previously pending claims lack enablement in view of the available evidence. The Examiner also indicated that cartilage tissue has a cellular component and a protein matrix component. As detailed above, the claims have been limited to chondrocyte progenitor cells, and evidence is provided in which two types of chondrocyte progenitor cells are used (HBMSCs and hMSCs). The cellular component necessary for cartilage tissue generation is clearly provided in the amended claims. The evidence provided shows that the protein matrix component is synthesized around the chondrocyte progenitor cells in both the *in vitro* and *in vivo* methods.

It is urged that one of skill in the art would be able to practice the presently claimed methods without undue experimentation and that all the pending claims are fully enabled. Withdrawal of the rejection of the claims under 35 USC §112, first paragraph, as lacking an enabling disclosure, is thus respectfully requested.

Concluding Remarks

A Request for a Two Month Extension of Time, extending the deadline for responding to the Office Action to Monday, April 27, 2009 is submitted herewith.

Every effort has been made to put the pending claims in condition for allowance. Favorable reconsideration and early allowance of all the pending claims is respectfully requested.

Should the Examiner have any further concerns regarding this application, he is requested to telephone the undersigned at 206.382.1191.

Respectfully submitted,

Janet Sleath
Registration No. 37,007

April 27, 2009

SPECKMAN LAW GROUP PLLC
20601